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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/005,211	12/04/2001	Keith D. Allen	R-325	5578

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EXAMINER
QIAN, CELINE X

ART UNIT	PAPER NUMBER
1636	10

DATE MAILED: 06/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/005,211	ALLEN, KEITH D.	
	Examiner	Art Unit	
	Celine X Qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *10-13 and 20-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 14-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-24 are pending in the application.

Election/Restrictions

Applicant's election without traverse of Group I in Paper No. 9 is acknowledged.

Accordingly, claims 10-13 and 20-24 are withdrawn from consideration for being directed to non-elected subject matter. Claims 1-9 and 14-19 are currently under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3-9 and 14-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a homozygous knockout mouse comprising a disruption in the PKDL2 gene which result in no production of the PKDL2 protein, wherein said mouse exhibits phenotypic features including increased activity, as compared to a wild type mouse, a method of producing such a transgenic mouse by homologous recombination in mouse ES cell, and a cell isolated from said female knockout mouse, does not reasonably provide enablement for other transgenic and/or knockout animal comprising any disruption in the PKDL2 gene. Further, the specification is not enabling for a knockout mouse comprising any disruption in the PKDL2 gene and for any cell comprising any type of disruption in a PKDL2 gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the Invention:

Claims 3-9 and 14-19 are drawn to a cell comprising a disruption in a PKDL2 gene, a non-human transgenic animal comprising a disruption in a PKDL2 gene, a cell isolated from said transgenic animal, a method of producing a transgenic mouse with any disruption in the said gene. Thus, the nature of the invention is directed to transgenic animals and methods of producing said transgenic animals.

Breadth of Claims:

In the instant case, the claims 3-9 and 14-19 encompass any transgenic animal containing any disrupted allele for the gene that encodes the PKDL2. Further, the claims encompass both heterozygous and homozygous knockout mouse comprising any disruption in the PKDL2 gene and exhibiting the phenotypes of hyperactivity as compared to wild type mice. Further, the claims encompass any cell comprising any disruption in the PKDL2 gene and method of producing PKDL2 knockout mouse by using any type of cell comprising a disruption of the PKDL2 gene. The disruption, as disclosed in the specification (page 7, lines 13-22) includes any

insertion, deletion or substitution in any portion of the gene (introns, exons, regulatory regions). The claims, therefore, encompass all such disruptions and also cover all animals that contain the PKDL2 gene disruption (page 7, lines 13-22 and 26-30).

The specification does not provide an enabling disclosure for the full scope of transgenic animals of the type claimed. The only embodiment enabled by the specification within the scope of claims 3-9 and 14-19 is for a homozygous knockout mouse comprising a disruption in the PKDL2 gene which result in no expression of the protein, wherein said mouse exhibits phenotype of hyperactivity as compared to wild type mice, a method of producing such a transgenic mouse, and a cell isolated from the knockout mouse. Thus the breadth of the claims is very broad and encompasses any transgenic animal and a knockout mouse with any disruption in the PKDL2 gene and includes any and all mutant forms, substitutions, deletions, or insertions in the PKDL2 gene.

Amount of guidance in the specification and Working Examples:

The specification discloses a PKDL2 transgenic knockout mouse, wherein the homozygous knockout mouse exhibits phenotype of hyperactivity as compared to wild type mice.

The specification and the working examples provide sufficient guidance to use the invention of a homozygous knockout mouse comprising a disruption the PKDL2 gene which result in no expression of the protein, wherein said mouse exhibits phenotypic features including hyperactivity as compared to wild type mice. The specification does not teach how to make and use the invention with other species of transgenic or knockout animals and with any knockout mouse with any form of disruption in the gene encoding PKDL2 protein, as claimed in the

claims 3-10 and 14-19. Neither does the specification teach how to make a PKDL2 transgenic knockout mouse by using homologous recombination using any type of cells. Further, the specification does not teach how to make and use any cell comprising any type of disruption in the PKDL2 gene as claimed. Moreover, the specification does not teach how to use transgenic mice having PKDL2 gene disruption but without any phenotype. The scope of claims 3-9 and 14-19 thus surpasses that enabled by the specification.

State of the Art, Predictability or Unpredictability of the art, Amount of experimentation necessary and Skill level of the artisan:

Although the skill of an artisan in this subject area is considered to be very high, it would require undue experimentation on the part of an artisan to make and use the claims as specified and use the invention with any and all transgenic animals as claimed. The specification and the working examples provide sufficient guidance to practice the invention with only a female homozygous knockout mouse comprising a disruption the PKDL2 gene which result in no expression of the protein, wherein said mouse exhibits phenotypic features including hyperactivity as compared to wild type mice. However, neither the specification nor the working examples provide enough guidance on how to practice the invention with any and all transgenic animals and/or transgenic mice carrying any and all transgene(s) of the types recited in the claims.

When considering the predictability of this invention, one has to remember that many of the phenotypes examined in transgenic and knockout models are influenced by the genetic background in which they are studied and the effect of allelic variation and the interaction between the allelic variants (pg.1425, paragraph 1 in Sigmund, C.D. 2000. Arterioscler Thromb

Vasc Biol.20:1425-1429). The specification only discloses the phenotype of a homozygous female PKDL2 gene knockout mouse but fails to disclose the phenotypes of any and all knockout animals with a disruption in the PKDL2 gene. Given the state of the art, the phenotype of any transgenic or knockout animal is unpredictable. Thus, the specification, in the instant case, is not enabling for transgenic and/or knock out animals, including mice, that exhibit no phenotype or that exhibit transgene-dependent phenotypes other than that disclosed in the instant specification.

Further, the transgene expression and the physiological consequences of transgene products are not always accurately predicted in transgenic mouse studies (pg.62, paragraph1, lines 7-9 in Wall, R.J. 1996. Theriogenology 45:57-68). Thus, the disclosure, while being enabling for a female homozygous knockout mouse containing two disrupted alleles for the gene encoding the PKDL2, does not provide sufficient support to predict the same phenotype in other animal systems.

The particular genetic elements required for expression varies from species to species. Our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior (Wall, 1996). Therefore, the phenotype of knockout animals is not predictable. For example, Jacks et al. (1992) describe Rb knockout mice that do not display retinoblastoma; rather they exhibit the unexpected phenotype of pituitary tumors. The pituitary tumors arise from cells lacking a wild-type Rb allele. Thus, tumors were found to arise not in retinas, as in humans, but in the pituitary gland (page 299, Discussion, paragraphs 1 and 3). Therefore, in the absence of specific guidance and working examples, the phenotype of transgenic animals with the scope as claimed is unpredictable. In such a situation, one skilled in

the art would not know how to make and use the invention as claimed, without undue experimentation.

The specification fails to provide an enabling disclosure for the preparation of other species of knockout animals besides mice having a disruption in the PKDL2 gene because the guidance offered in the specification is limited to the preparation of mice harboring such mutations and no teachings or guidance are offered in regard to how one would have prepared any other type of animal having the recited gene disruption. Since homologous recombination is required for gene targeting methods such as employed in the instant invention, embryonic stem (ES) cell technology must be available to carry out the method. The prior art does not teach the generation of a transgenic mouse from any other types of cells. The only species in which such technology was known was the mouse and the artisan did not accept that it was possible to have prepared ES cells in other species (see e.g. Bradley et al., paragraph bridging pages 537-538). Campbell and Wilmut, 1997 acknowledge reports of ES-like cell lines in a number of species, but emphasize that as yet there are no reports of any cell lines which contribute to the germ line in any species other than the mouse (p. 65). Likewise, Mullins et al. (1996) teach that "[a]lthough to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated. This remains a major goal for the future and may well require the use of novel strategies which depart widely from the traditional methods used in the mouse" (p. S38, column 1, paragraph 1). Thus, knockout animals cannot be prepared for any species other than the mouse. Since ES cell technology was required to produce the claimed animals and practice the claimed methods of using such animals, in the absence of such technology available in other

species, one skilled in the art would have been required to exercise undue experimentation to produce the claimed animals and to practice the claimed methods in species other than mice.

In view of the limited guidance in the specification, and limited working examples directed to transgenic, knockout mice with a specific knockout gene and exhibiting a specific phenotype, and the unpredictability of the art, one skilled in the art would be required to engage in undue experimentation, in order to make and use the invention in its full scope as claimed. Thus, the enabled scope of the claims is limited to a homozygous knockout mouse comprising a disruption the PKDL2 gene which result in no expression of the protein, wherein said mouse exhibits phenotype of hyperactivity as compared to wild type mice.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 8, 14 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 1 and 2, the term "selectable marker," renders the claims indefinite because it is unclear how a marker protein can be part of a vector construct. It is recommended to use terms such as "selectable marker gene."

In addition, it is unclear how the target construct is arranged. In other words, is the first polynucleotide adjacent to the second polynucleotide or there is a selectable marker gene in between? In addition, it is also unclear whether the first and second polynucleotide is a

contiguous sequence of the target gene or just portions of the target gene. The arrangement of the elements is essential to the operability of the invention.

Regarding claims 8 and 15, the word "derived" renders the claim indefinite because the nature and number of derivative processes is unknown. Use of the term "isolated" is suggested.

Regarding claim 14, the term "significant expression" renders the claim indefinite because it is unclear what level of expression is considered to be significant. As such, the metes and bounds of the claim cannot be established.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mansour et al. (1988, Nature, vol. 336, No. 24, 348-352), in view of Guo et al. (AF).

Mansour et al. teach a strategy for targeted disruption of the hprt gene and proto-oncogene int-2 in mouse embryonic stem cells and subsequent generation of knockout mice. Their teaching addresses the previous technical difficulty of obtaining embryonic stem cell carrying non-selectable, targeted gene mutation at loci of interest, and therefore provides a model which can be used to produce homozygous mutation of any gene, regardless of its function, if a cloned fragment of the gene is available (see page 348, second paragraph, line 1-3, third paragraph, line 1-5, and page 352, fourth paragraph, line 1-3). Mansour et al. further teach the

generation of two targeting constructs, pRV9.1/TK and pINT-2-N/TK, each contains two sequences from an hprt gene and an int-2 gene respectively, and a neo selection marker gene in between the two sequences (see page 350, figure 3). However, Mansour et al. do not teach how to make a PKDL2 target construct and knockout mouse.

Guo et al. teach that mutations in PKD1, PKD2, PKDL and REJ are four known member of polycystins that share significant homology with each other (see page 241, 1st col. lines 1-4). Guo et al. teach the cloning and characterization of a novel polycystin family member PKDL2 in mouse and human. Guo et al. further provide the nucleic acid sequence encoding Guo et al. teach the cloning and characterization of a novel polycystin family member PKDL2 (see page 243, Figure 1). Guo et al. teach that knockout mouse models of PKD1 and PKD2 illustrate their critical role in the development of kidney and pancreas. Guo et al. also teach that PKDL2 belong to PKD2 subgroup and share structural homology with cation channels such as voltage gated Ca+, Na+ and K+ channel families. Guo et al. further teach that PKDL2 might be implicated in 5q syndrome.

It would have been obvious to one of ordinary skill in the art at the time of filing to make a PKDL2 knockout construct and a transgenic knockout mouse because of the combined teachings of Mansour et al. and Guo, which provide a general method of making targeted disruption of specific gene in mouse genome to study its function and the importance in studying the PKDL2 function. The ordinary artisan would have been motivated to do so to study the precise role PKDL2 plays in facilitate membrane permeability or whether it has any implication in 5q syndrome. The level of skill in the art of making gene targeting constructs and subsequently generating knockout mouse is high, absent evidence to the contrary, one of

ordinary skill in the art would have reasonable expectation of success to make a PKDL2 knockout construct and generate a PKDL2 knockout mouse as claimed. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D.
May 30, 2003

JAMES KETTER
PRIMARY EXAMINER